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(54) Title: COMPOSITIONS AND METHODS FOR COMBINATION ANTIVIRAL THERAPY

(57) Abstract: The present invention relates to therapeutic combinations of [2-(6-amino-purin-9 yl)-1-methyl-ethoxymethyl]-phosphonic acid diisopropoxycarbonyloxymethyl ester (tenofovir disoproxil fumarate, Viread®) and (2R, 5S, cis)-4-amino-5-fluoro-1-(2 hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine, Emtriva™, (-)-cis FTC) and their physiologically functional derivatives. The combinations may be useful in the treatment of HIV infections, including infections with HIV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors. The present invention is also concerned with pharmaceutical compositions and formulations of said combinations of tenofovir disoproxil fumarate and emtricitabine, and their physiologically functional derivatives, as well as therapeutic methods of use of those compositions and formulations.





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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, INSPEC, CHEM ABS Data, EMBASE, WPI Data, PAJ

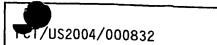
Category °	Citation of document, with indication, where appropriate, of	Relevant to claim No.	
X	RISTIG MARIA B ET AL: "Tenof disoproxil fumarate therapy f hepatitis B in human immunode virus/hepatitis B virus-coinf individuals for whom interfer lamivudine therapy have faile JOURNAL OF INFECTIOUS DISEASE vol. 186, no. 12, 15 December 2002 (2002-12-15) 1844-1847, XP002284897 ISSN: 0022-1899 abstract page 1844, column 2, second 1 paragraph: "Subjects" page 1845, column 2, last par "Discussion"	or chronic ficiency ected on-alpha and d." S, , pages	1-58
Special cat docume conside earlier d filing de docume which is cluston docume other m docume later the	nt which may throw doubts on priority claim(s) or s cited to establish the publication date of another or other special reason (as specified) nt referring to an oral disclosure, use, exhibition or	*T* later document published after the interest or priority date and not in conflict with cited to understand the principle or the invention *X* document of particular relevance; the considered novel or cannot be considered novel or cannot involve an inventive step when the document of particular relevance; the considered to involve an inventive step when the document is combined with one or moments, such combined with one or moments, such combination being obvious in the art. *8* document member of the same patent for the same patent of	mational filing date the application but tory underlying the laimed invention be considered to laimed invention the taken alone laimed invention the entive step when the re other such docu- s to a person skilled amily ch report

INTERNATIONAL SEARCH REPORT



tion) DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	
	Relevant to claim No.
MURRY, JEFFREY P. ET AL: "Reversion of the M184V mutation in simian immunodeficiency virus reverse transcriptase is selected by tenofovir, even in the presence of lamivudine" JOURNAL OF VIROLOGY, 77(2), 1120-1130 CODEN: JOVIAM; ISSN: 0022-538X, 12 January 2003 (2003-01-12), XP002284898 page 1126, figure 2 page 1129, column 1, paragraph 2	1-58
"Anti-HIV drug updates—three drugs on the near horizon." PROJECT INFORM PERSPECTIVE. JAN 2003, no. 35, January 2003 (2003-01), pages 4-7, XP001181983 page 6, column 2, paragraph 3 - page 7, column 2, paragraph 3	1-58
FUNG HORATIO B ET AL: "Tenofovir disoproxil fumarate: A nucleotide reverse transcriptase inhibitor for the treatment of HIV infection." CLINICAL THERAPEUTICS, vol. 24, no. 10, October 2002 (2002-10), pages 1515-1548, XP002285091 TSSN: 0149-2918	2,3,32, 33,43-58
page 1533, column 1, paragraph 2 page 1542,table VIII	1,4-31, 34-42
MULATO A S ET AL: "ANTI-HIV ACTIVITY OF ADEFOVIR (PMEA) AND PMPA IN COMBINATION WITH ANTIRETROVIRAL COMPOUNDS: IN VITRO ANALYSES" ANTIVIRAL RESEARCH, ELSEVIER SCIENCE BV., AMSTERDAM, NL, vol. 36, no. 2, November 1997 (1997-11), pages 91-97, XP000890091 ISSN: 0166-3542	1,4-31, 34-42
page 93, column 2, paragraph 2 - page 95, column 1, paragraph 2 page 94, figure 1	2,3,32, 33,43-58
WO 00/25797 A (BARRY DAVID; ROUSSEAU FRANCK (US); FURMAN PHILLIP A (US); PAINTER GEO) 11 May 2000 (2000-05-11) page 5, line 5-12 page 15, lines 1-24 claims 5, 10 and 20	25-31, 34-42
	immunodeficiency virus reverse transcriptase is selected by tenofovir , even in the presence of lamivudine" JOURNAL OF VIROLOGY , 77(2), 1120-1130 CODEN: JOVIAM; ISSN: 0022-538X, 12 January 2003 (2003-01-12), XP002284898 page 1126, figure 2 page 1129, column 1, paragraph 2 "Anti-HIV drug updates—three drugs on the near horizon." PROJECT INFORM PERSPECTIVE. JAN 2003, no. 35, January 2003 (2003-01), pages 4-7, XP001181983 page 6, column 2, paragraph 3 - page 7, column 2, paragraph 3 FUNG HORATIO B ET AL: "Tenofovir disoproxil fumarate: A nucleotide reverse transcriptase inhibitor for the treatment of HIV infection." CLINICAL THERAPEUTICS, vol. 24, no. 10, October 2002 (2002-10), pages 1515-1548, XP002285091 ISSN: 0149-2918 page 1533, column 1, paragraph 2 page 1542,table VIII MULATO A S ET AL: "ANTI-HIV ACTIVITY OF ADEFOVIR (PMEA) AND PMPA IN COMBINATION WITH ANTIRETROVIRAL COMPOUNDS: IN VITRO ANALYSES" ANTIVIRAL RESEARCH, ELSEVIER SCIENCE BV., AMSTERDAM, NL, vol. 36, no. 2, November 1997 (1997-11), pages 91-97, XP000890091 ISSN: 0166-3542 page 93, column 2, paragraph 2 - page 95, column 1, paragraph 2 page 94, figure 1 WO 00/25797 A (BARRY DAVID; ROUSSEAU FRANCK (US); FURMAN PHILLIP A (US); PAINTER GEO) 11 May 2000 (2000-05-11) page 5, 11ne 5-12





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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	RICHMAN D D: "Antiretroviral activity of emtricitabine, a potent nucleoside reverse transcriptase inhibitor." ANTIVIRAL THERAPY. JUN 2001, vol. 6, no. 2, June 2001 (2001-06), pages 83-88, XP009032162 ISSN: 1359-6535 page 84, column 2, second last paragraph -	2,3,32, 33,43-58
_	page 85, column 1, paragraph 2	34-42
A	DE CLERCQ ERIK: "New anti-HIV agents and targets" MEDICINAL RESEARCH REVIEWS, vol. 22, no. 6, November 2002 (2002-11), pages 531-565, XP002284899 ISSN: 0198-6325 page 541, paragraph 3 - page 542, paragraph 5	1-58

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONA EARCH REPORT

Te17US2004/000832	

Patent document clted in search report		Publication date		Patent family member(s)	Publication date
WO 0025797	A	11-05-2000	AU CN EP EP ID JP WO US	1810600 A 1329497 T 1380303 A1 1382343 A1 1124562 A1 29471 A 2002528508 T 0025797 A1 2003158150 A1 6528515 B1	22-05-2000 02-01-2002 14-01-2004 21-01-2004 22-08-2001 30-08-2001 03-09-2002 11-05-2000 21-08-2003 04-03-2003